

NEUROPSYCHOLOGY OF DIABETES MELLITUS

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Cautionary Tale

- ▣ 23 yo AA woman with insulin dependent DM; worked as KP emergency room receptionist; she lived 2 blocks away from ED
- ▣ Referred to Psych because of excessive hospital utilization; 10 episodes in past year of hypoglycemic coma
- ▣ If she did not show up for work shift, ED staff would co-dependently go to her apartment
- ▣ Refused to consistently self treat or tell family or boyfriends that she was diabetic because she believed that this would lead to never being able to get married
- ▣ After 1 session with me, she failed to appear for 2nd session because she died of final hypoglycemic event.

“Suicide” Attempt in Diabetic Pt

- ▣ Need to be aware of whether ER patients are diabetic
- ▣ Diabetics often have cognitive deficits
- ▣ Can miscalculate insulin dosages and accidentally overdose

What is 'metabolic syndrome'?

- ▣ Abdominal obesity (fat belly)
- ▣ Impaired glucose metabolism (diabetes, pre-diabetes)
- ▣ High “bad” cholesterol (LDL) or low “good” cholesterol (HDL)
- ▣ High blood pressure

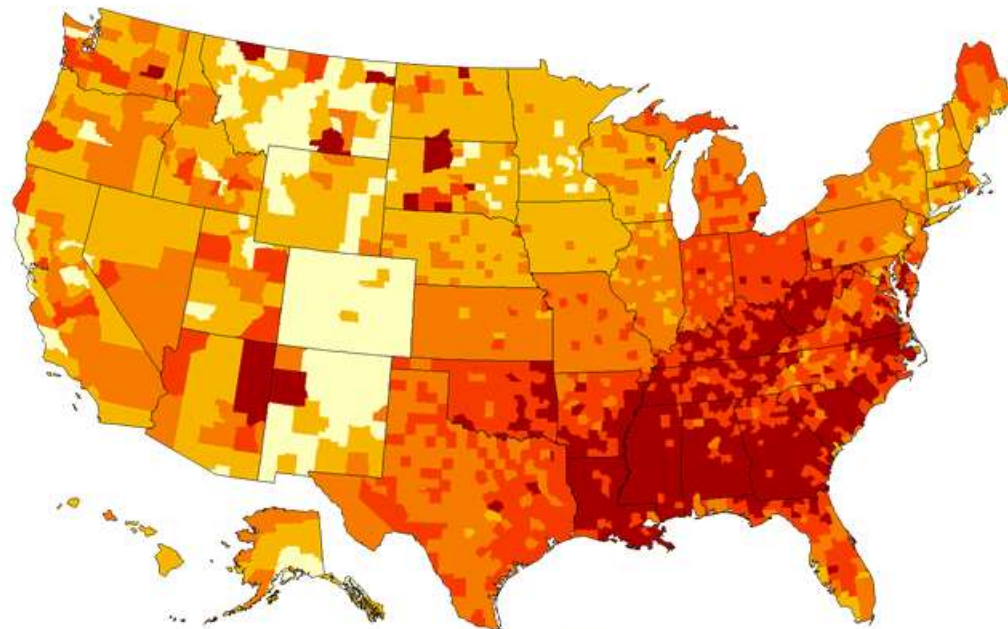
- ▣ Each metabolic syndrome factor independently increases stroke risk
- ▣ Having all 4 doubles dementia risk

Metabolic Control

- ▣ Daily blood glucose tests
- ▣ Cholesterol management
- ▣ Blood pressure management
- ▣ Healthy diet and weight

CDC: Deep red = counties with 11.2 % diagnosed with diabetes

2008 Age-Adjusted Estimates of the Percentage of Adults[†] with Diagnosed Diabetes



Download data: [Excel](#) | [PPT](#)

Download all maps: [PPT](#)

[Data Dictionary](#)

[Methodology](#)

National average of 8.3 percent

Diabetes Belt

The 644 counties in the diabetes belt match up to known risk factors for the disease, including

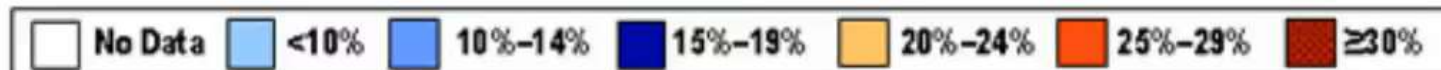
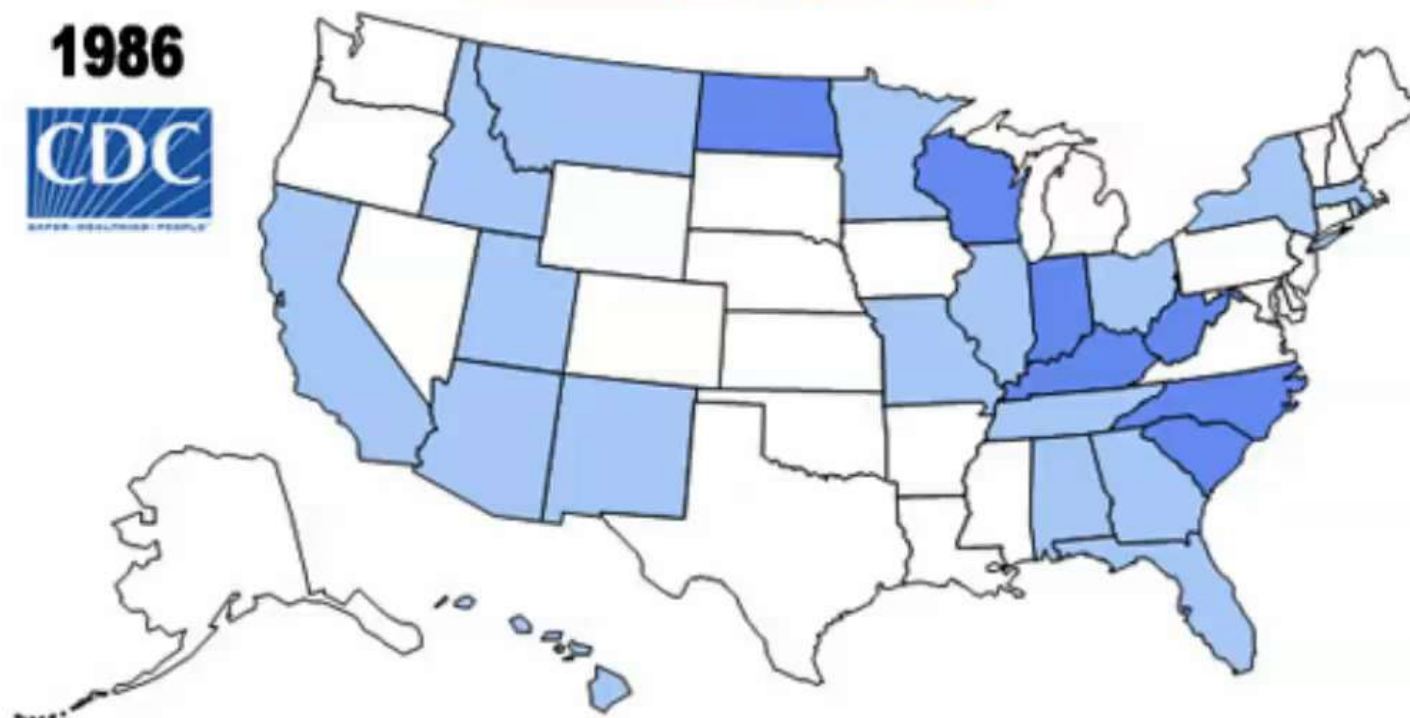
- ▣ a high obesity rate (33% vs. 26% nationally);
- ▣ sedentary lifestyles (31% vs. 25%);
- ▣ lower education levels (24% with college degrees vs. 34%)
- ▣ more non-Hispanic blacks (24% vs. 9%).
- ▣ Highly tied to high consumption of fried foods, processed foods, sugar use, and lack of exercise

CDC Obesity (BMI >30)
1986-2010

Percent of Obese (BMI ≥ 30) in U.S. Adults

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1986

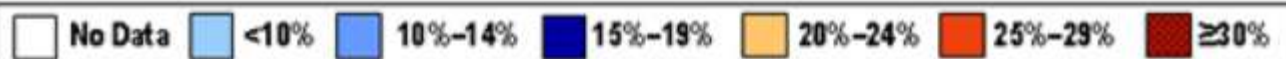
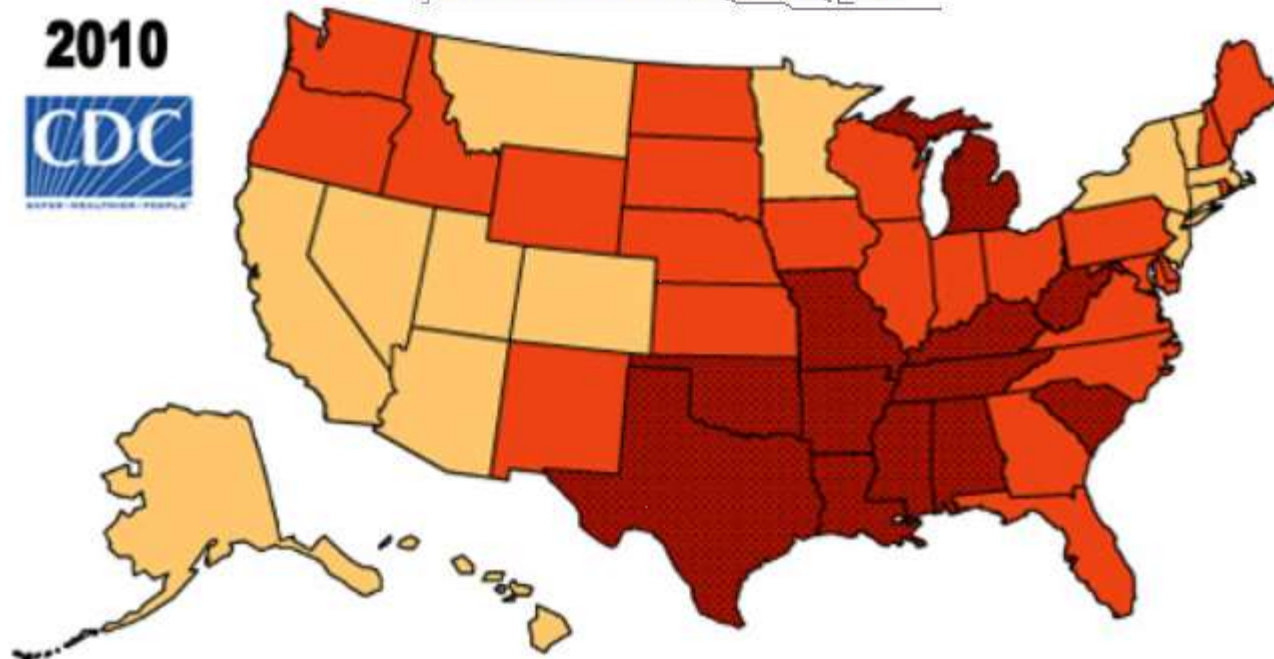


CDC % Obesity in US Adults

Percent of Obese (BMI ≥ 30) in U.S. Adults

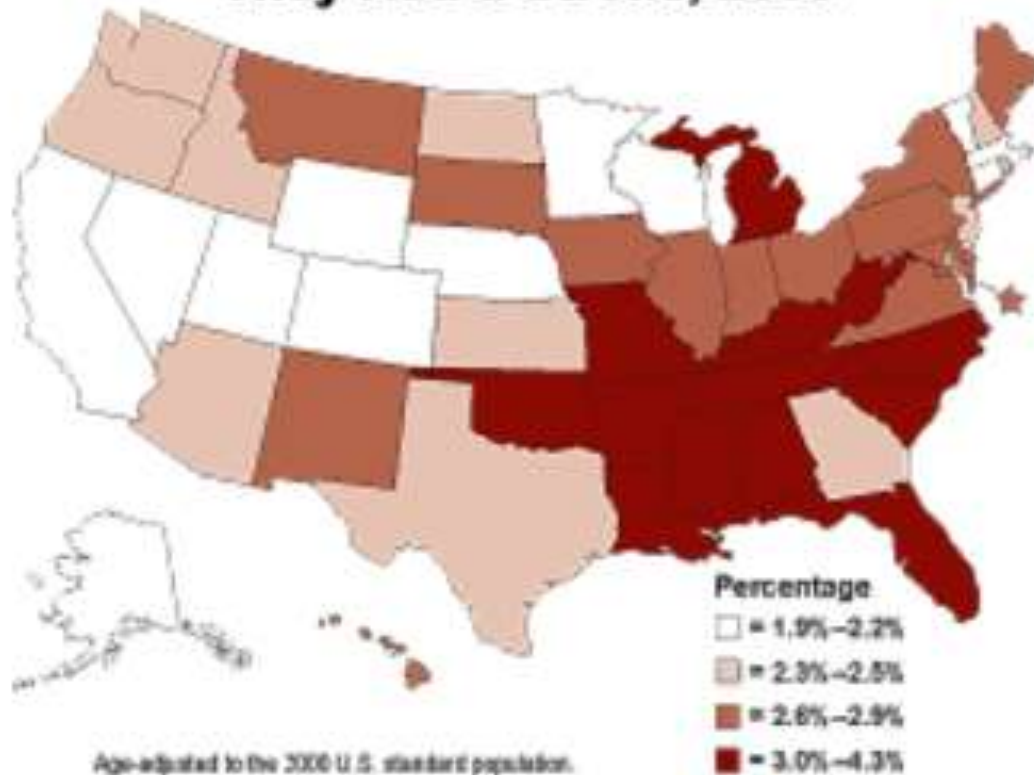
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2010



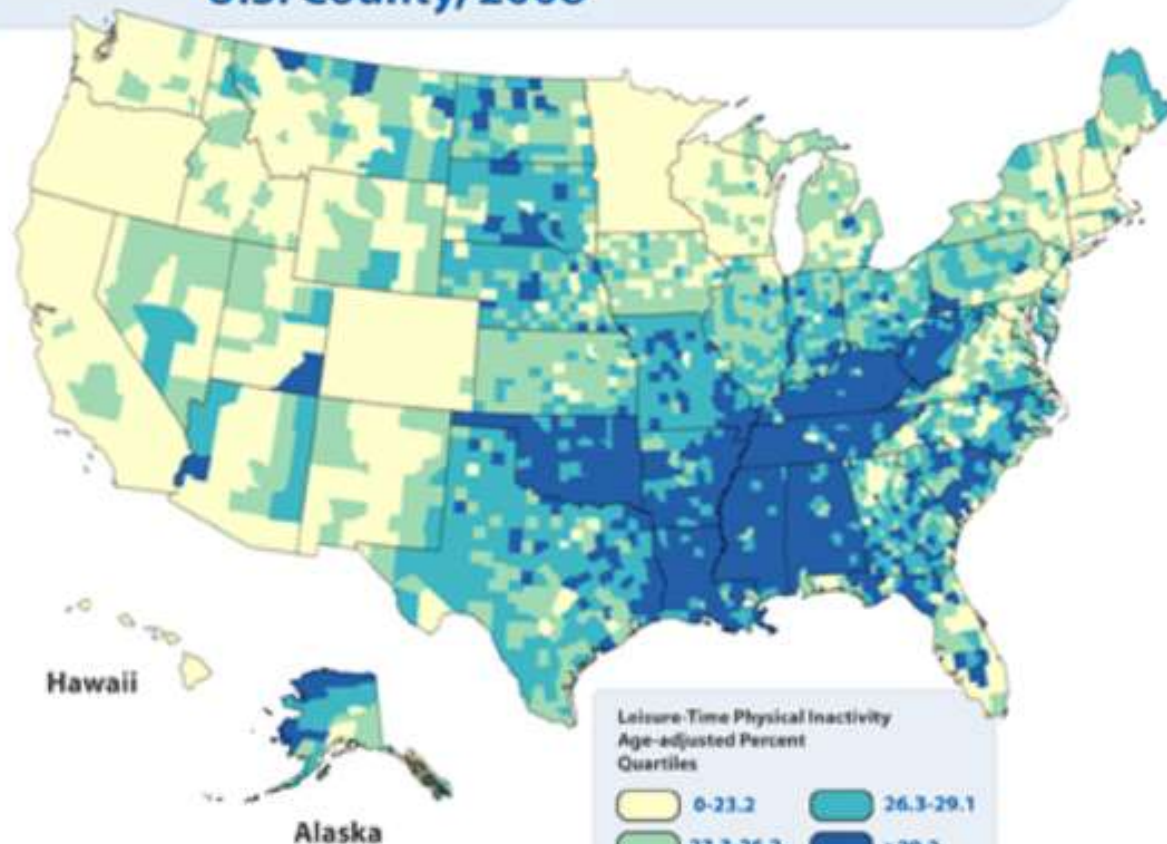
CDC % Stroke

Percentage of People Who Were Ever Told They Had a Stroke, 2008



CDC Physical Inactivity

**Leisure-Time Physical Inactivity by
U.S. County, 2008**



Diabetes

- ▣ Diabetes mellitus is a metabolic disease characterized by high blood glucose levels (hyperglycemia).
- ▣ Diabetes has been diagnosed in 20% of American adults, and the vast majority have Type 2.
- ▣ Diabetes effects the human body:
 - heart
 - circulation
 - kidneys
 - eyes
 - peripheral nervous system
 - brain

Diabetes Mellitus

- ▣ Type 1: (absolute deficiency of insulin secretion, insulin-dependent, juvenile onset)
 - Traditionally early onset

- ▣ Type 2: (non-insulin dependent), about 90%
 - Development of insulin resistance and inadequate compensatory insulin secretion response
 - Average onset = age 60

Brain needs steady glucose

- ▣ Brain = 20% of the body's metabolic consumption and is obliged to use glucose exclusively as its fuel.
- ▣ Normal brain functioning is dependent upon sufficient levels of continuous circulating glucose.
- ▣ Diabetic fluctuations in blood glucose levels can affect brain functioning.
- ▣ Starved of glucose, brain functions suffer: thinking and mood decline.

Classic DM Medical Consequences

- ▣ Retinopathy with potential loss of vision
- ▣ Nephropathy leading to renal (kidney) failure
- ▣ Peripheral neuropathy with risk of foot ulcers and amputations
- ▣ Autonomic neuropathy causing GI, genitourinary, and CV sx's, and sexual dysfunction
- ▣ Increased incidence of atherosclerotic cardiovascular, peripheral arterial, & cerebrovascular disease
- ▣ Increased mortality

Hypoglycemia

- ▣ If profound starvation→ coma, seizure, and (rarely) severe brain damage.
- ▣ Hypoglycemia:
 - 1-2% of deaths among diabetic patients,
 - Still much lower than the mortality from diabetic ketoacidosis (6%) (a severe accumulation of keto acids so that the pH of the blood is substantially decreased)
- ▣ Severe episodes = third party help needed.

The Problem

- ▣ Strict blood sugar control :
 - has the great benefit of reducing target organ damage (retinopathy, nephropathy, and neuropathy)
 - but brings with it a threefold increase in severe hypoglycemia.

Brain Sxs of Hypoglycemia

- ▣ Hunger
- ▣ Nervousness and shakiness
- ▣ Perspiration
- ▣ Dizziness or light headedness
- ▣ Sleepiness
- ▣ Confusion
- ▣ Difficulty speaking
- ▣ Feeling anxious or weak
- ▣ Headache
- ▣ Lack of energy
- ▣ Inability to concentrate
- ▣ Prolonged severe hypoglycemia may result in a hypoglycemic coma.

Brain sxs of Hyperglycemia

- ▣ Thirst
- ▣ Frequent urination
- ▣ Vomiting
- ▣ Drowsiness
- ▣ Abdominal pain
- ▣ Pain in the legs
- ▣ Fatigue
- ▣ Impaired cognitive functioning
- ▣ Depressive mood
- ▣ Anxiety
- ▣ Prolonged severe hyperglycemia may result in ketoacidosis.

DM & Cognition

- ▣ DM can effect thinking
- ▣ 1922: 1st medical NP study, Miles & Root:
 - DM had shorter memory span and slower sustained attention

Diabetes & the Brain

- ▣ Cerebral complications of DM are referred to as “diabetic encephalopathy”.

- ▣ Diabetes:
 - may speed up aging-related cognitive deficits

 - Causes twofold increase in the risk of dementia in type 2 DM.

Diabetes & the Brain 2

- ▣ Type 2 diabetes more often produces some
type of cognitive problem
- ▣ Most significant deficits are on tasks of
 - executive function
 - speed of processing
 - memory in Type 2 DM

Diabetes and Cognitive deficits

- ▣ How diabetes causes cognitive deficits is still a scientific mystery

Diabetes and Dementia: Mechanisms

• co-morbidity
• medication

• genetic
predisposition

Underlying Mechanisms

Macrovascular
disease

• brain infarcts

Stroke

Microvascular
disease

• insidious
ischemia
• microinfarcts

Glucose
toxicity

• inflammation
• advanced protein
glycation
• oxidative stress

Insulin

↑ secretion
↓ breakdown of
 β amyloid

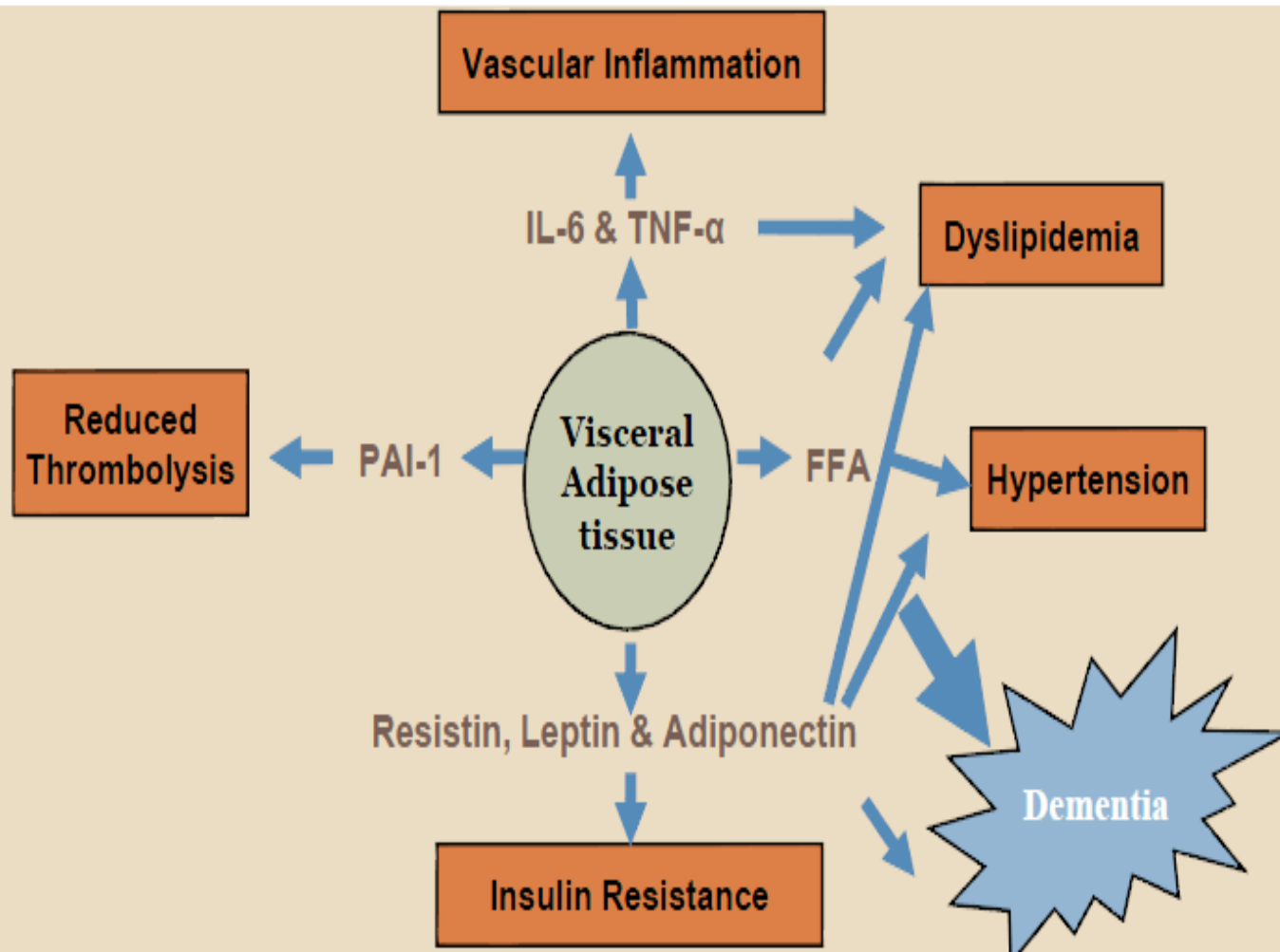
Brain Pathology

Vascular dementia

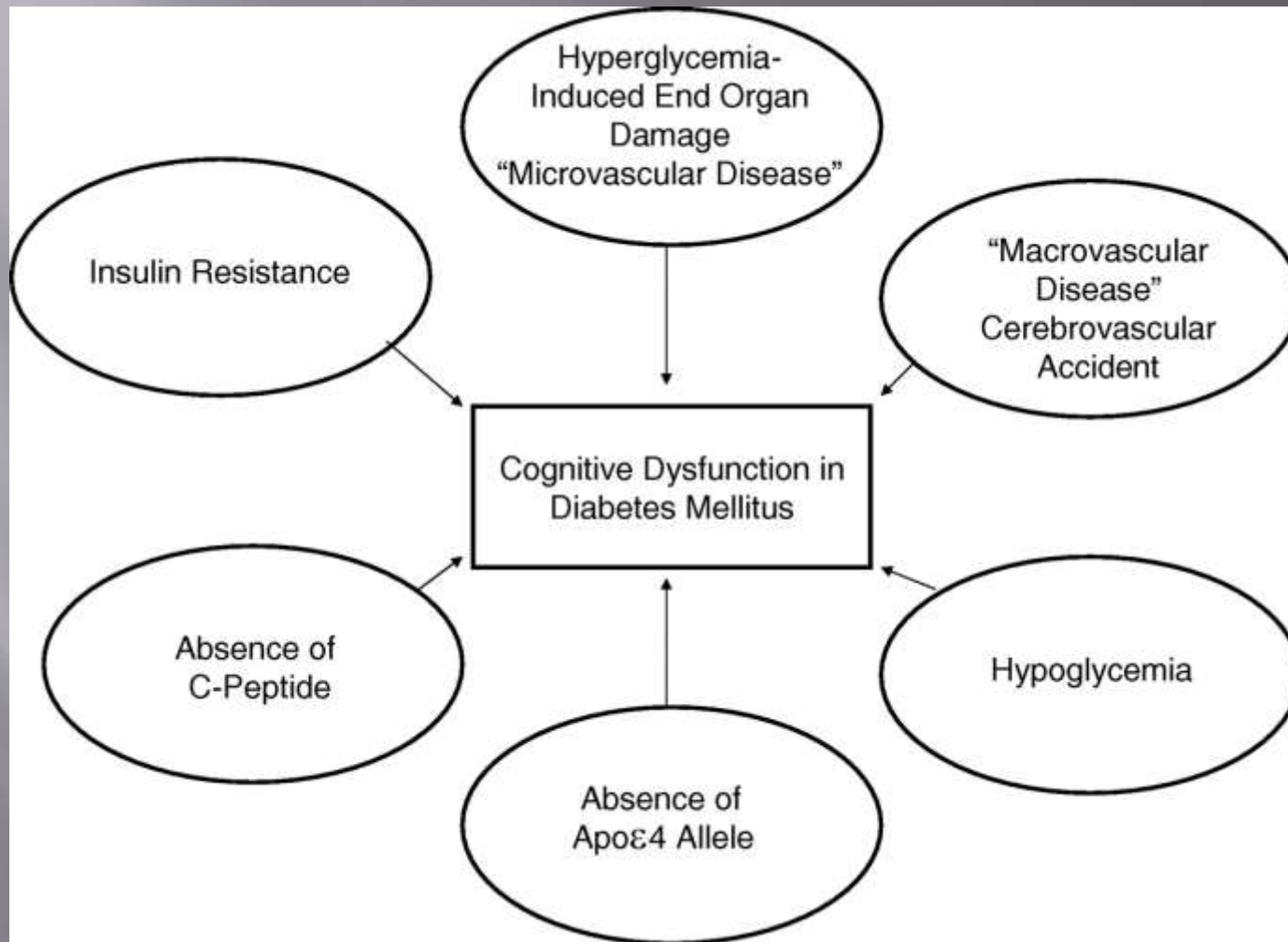
Accelerated aging

Alzheimer disease

Mechanisms linking Obesity to Dementia



Summary of possible mechanistic contributors to cognitive dysfunction seen in diabetes mellitus



Kodl, C. T. et al. Endocr Rev 2008;29:494-511

ENDOCRINE
REVIEWS

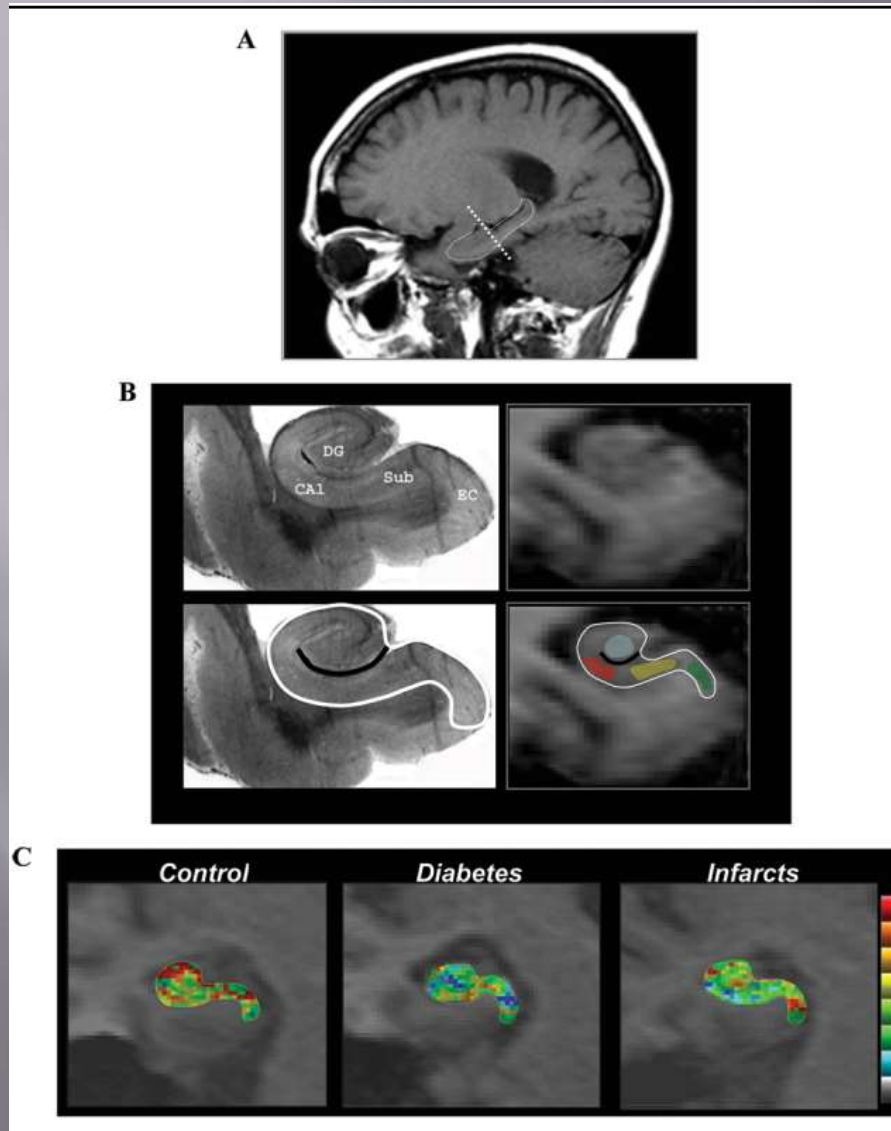
Hippocampus: Index to Memory



Hippocampus (outlined in red) is involved in learning and memory.

Repeated episodes of high or low blood sugar → → leads to reduced memory functioning.

AD & DM affect Hippocampus differently



- Diabetes & infarcts related to hippocampal dysfunction
- Dentate gyrus linked to diabetes & blood glucose levels
- CA1 & subiculum linked to infarcts & transient hypoperfusion;
- AD targets entorhinal cortex
- Normal blood glucose levels increase dentate function, i.e. via exercise

Large Scale Epidemiologic Studies: DM is a problem for your brain

- ▣ DM is associated with increased risk of cognitive dysfunction
 - Desmond, et al., 1993
 - Van Boxtel et al., 1998
 - Launer, et al., 1993
- Framingham Heart Study:
 - ▣ DM and HTN interact to produce cognitive deficits
 - ▣ If both DM and HTN: worst cognitive outcomes

Mechanisms for DM effects on Cognition

- ▣ Hypoglycemia
- ▣ Chronic hyperglycemia
- ▣ High Insulin Levels (what brain produces)
 - Brain produced Insulin increases with age
 - Increased insulin boosts levels of beta-amyloid.
 - Increased risk for AD

Insulin in the brain

- ▣ Insulin receptors are widely distributed in the brain, esp. in hypothalamus and hippocampus
- ▣ Hippocampus has high density of insulin receptors.
- ▣ Deterioration of insulin receptors are associated with AD and cognitive deficits in older type 2 DM
- ▣ This is reason why type 2 DM has more memory deficits than type 1 DM

Hyperglycemia & Cognitive Deficits

- ▣ Hyperglycemia leads to
 - microvascular abnormalities
 - cognitive deficits

- ▣ Presence of cardiovascular risk factors are important

Type 1 DM: Onset before age 5

- ▣ Earlier onset of DM is associated with greatly increased risk of hypoglycemia
 - Young kids lack verbal skills to tell you sxs

- ▣ Onset before age 5 and 1 or more severe hypoglycemic episodes:
 - 25% decline in cognitive abilities
 - Attention ↓
 - Developmental delays on Vocabulary & Block Design

Type 1 DM: Age 6-14 onset

- ▣ Onset age 6-14:
 - Do not have NP deficits:
 - ▣ except somewhat lower scores on verbal IQ and achievement tests
 - ▣ due to missing more school
 - Mild hypoglycemic events cause temporary attentional deficit
- ▣ Severe hypoglycemia can produce temporary:
 - Attention ↓
 - Memory ↓
 - Visual spatial ↓
 - EEG abnormalities

Chronic Hyperglycemia & Cognitive Dysfunction in Type 1 DM in adults

- ▣ Chronic high blood glucose levels lead to:
 - retinopathy,
 - peripheral neuropathy,
 - and CNS effects.

- ▣ Poor metabolic control (indexed by peripheral neuropathy) associated with deficits in:
 - Attention
 - Psychomotor speed
 - Spatial processing (effect sizes of .3-.4)

Type 1 DM: adult

- ▣ Relatively subtle or no cognitive impairment
- ▣ Deficits related to peripheral neuropathy and chronic hyperglycemia, or profound hypoglycemic episodes
- ▣ Peripheral neuropathy: strong relationship with cognitive ↓
- ▣ If poorly controlled: mild-moderate cognitive effect:
 - Processing Speed ↓ ↓
 - Attention ↓
 - Memory ↓
 - Visual spatial ↓
 - Executive ↓ (esp. if 15 years +)

Type 1 DM: adult

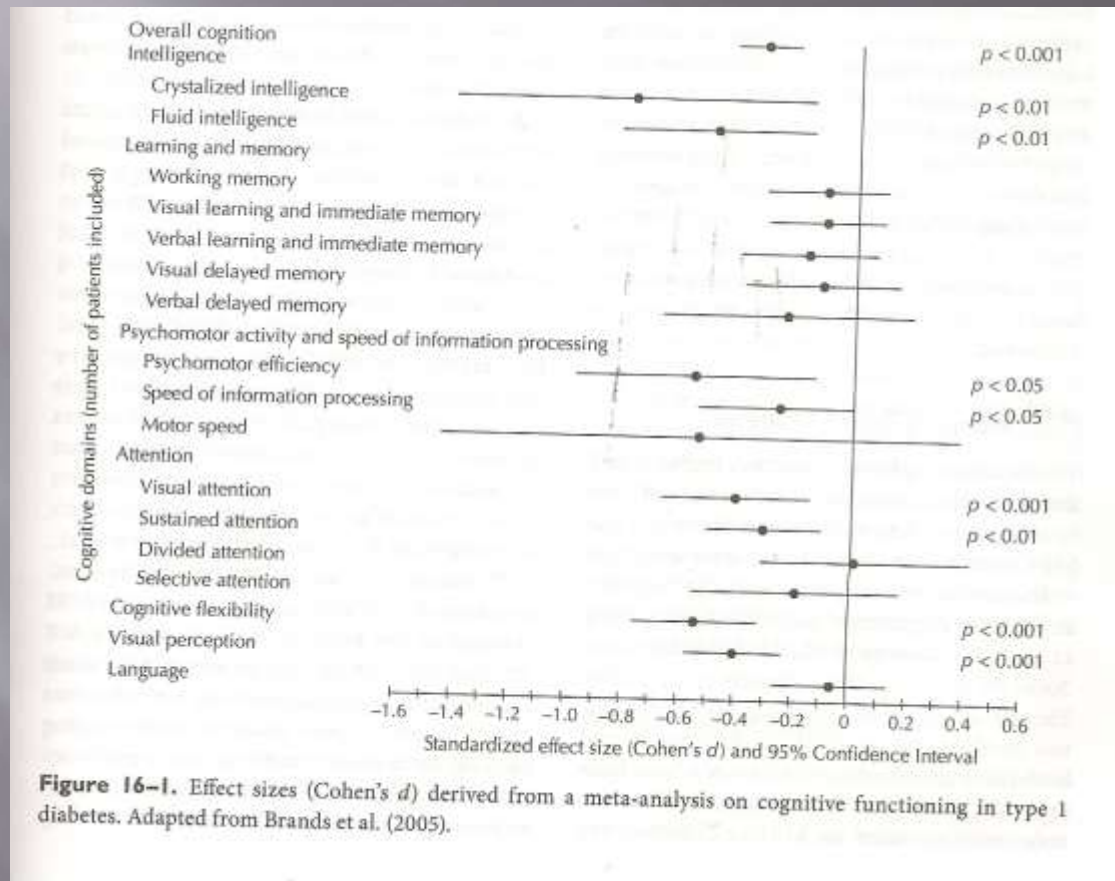
- ▣ Recurrent hypoglycemia:
 - Single profound hypoglycemic episode can produce brain damage
 - ▣ No role for hypoglycemia in the pathogenesis of cognitive deficits
 - ▣ Rate of severe hypoglycemic-induced cognitive impairment is unknown but relatively low in DM adults.
 - NP deficits (in cross sectional studies; 5 + episodes):
 - ▣ Visual spatial ↓
 - ▣ Psychomotor slowing
 - ▣ Fluid IQ ↓
 - ▣ Decision making ↓
 - No NP deficits in longitudinal studies of 13-39 y (both DCCT and Stockholm Diabetes Intervention studies)

Christopher Ryan, 2009

Type 1 DM adult

- Unclear why longitudinal vs. cross sectional results disagree.
- Animal studies: best predictor of brain damage is duration of hypoglycemia
- In stroke research, co-occurrence of hyperglycemia increases risk & magnitude of CNS damage
- Those with greatest hypoglycemia-induced cognitive deficits also have hx of chronic hyperglycemia

2010 Meta-analysis of Type 1 DM Cognition with age <50



Middle aged type 1 diabetics show mild cognitive deficits on wide range of neuropsychological tests relative to controls, esp. in processing speed and executive functioning. No difference between pts with and without recurrent severe hypoglycemic episodes.

Brands et al., 2005

Hyperglycemia in Type 1 DM adults

- ▣ Type 1 diagnosed before age 17
- ▣ Three cognitive deficits:
 - Attention
 - Processing speed
 - Visuospatial processing
- ▣ Best predictor of cognitive ↓↓: poor metabolic control (with peripheral neuropathy)
- ▣ Presence of diffuse lesions on MRI

Type 2 Diabetes

- ▣ Non insulin dependent Diabetes: development of insulin resistance, lowered beta cell function; chronic hyperglycemia
- ▣ Over 40, and BMI >25
- ▣ 90% of all diabetics
- ▣ Genetic
- ▣ A mean duration of 7 years in type 2 DM appears to have a similar effect on the brain as a mean duration of 30 years in type 1 DM (Brands et al., 2007)

Type 2 DM Cognitive picture

- ▣ Significant Cognitive ↓ (small to moderate effect sizes (.4-.8):
 - Learning & episodic memory most ↓
 - Processing speed
 - Executive Functioning deficits
- ▣ Normal Cognition: Visuospatial processing, attention, semantic klg, language ability
- ▣ Chronic hyperglycemia is best predictor of cognitive deficits; a consequence of poor metabolic control
- ▣ Often co-present CV disease (but DM effects independent)

Type 2 DM adult

- ▣ Alzheimer's Disease:
 - 2 x risk
 - Stronger risk when diabetes occurs at mid-life than in late life
 - Diabetics who take insulin or pills to help control their disease have a lower Alzheimer's risk.

- ▣ People with schizophrenia are at increased risk for type 2 DM (before antipsychotic medications, which also produce metabolic syndrome)

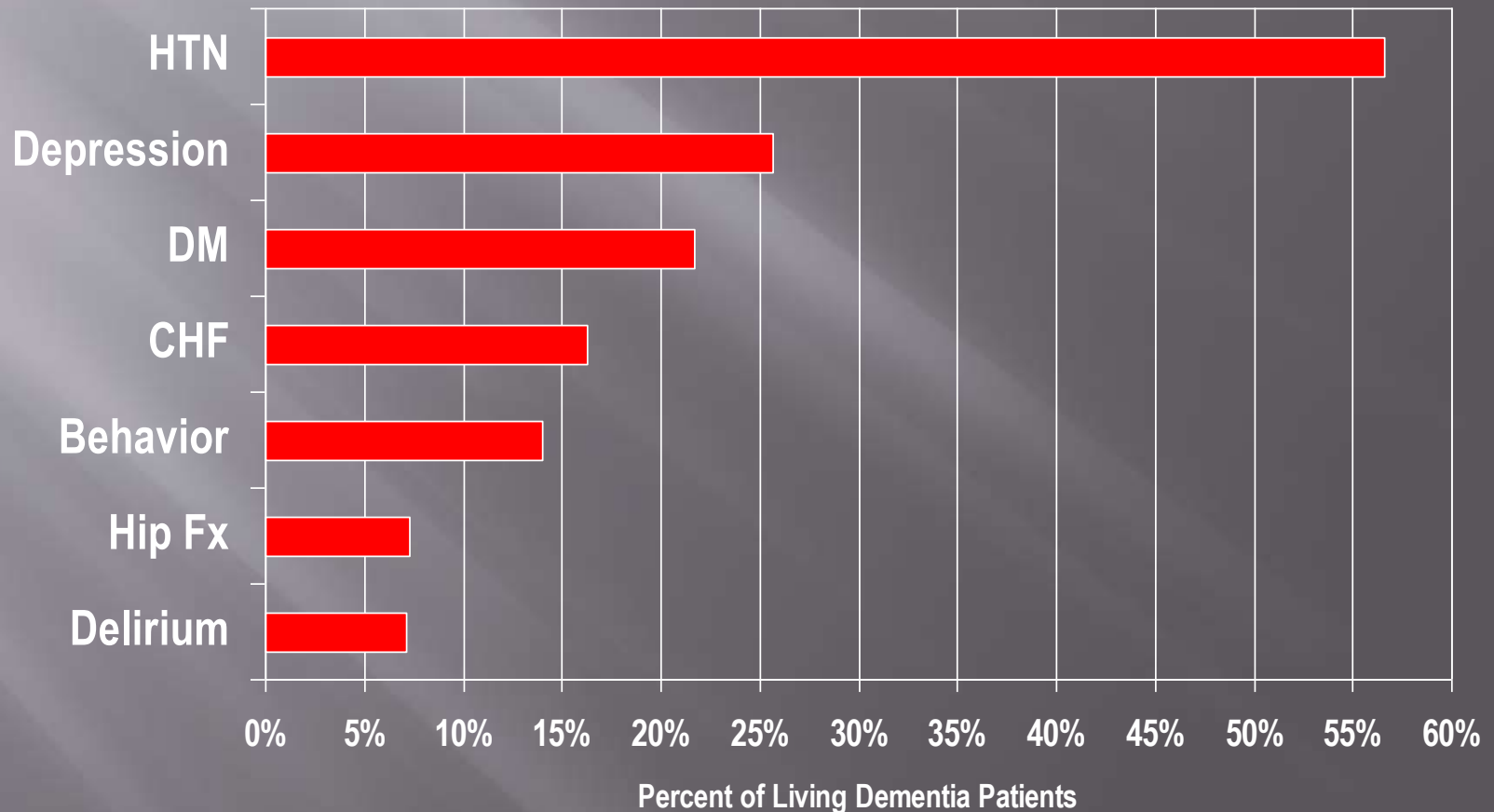
Type 2 DM Cognitive Correlates

- ▣ Are all Type 2 diabetics equally vulnerable to cognitive deficits?
- ▣ Age increases risk: Largest effects of type 2 DM on cognition is in older pts
- ▣ More likely to have CV disease (but DM effects independent)
- ▣ Brain atrophy correlates with HTN, CV disorders, DM, age, and medications
- ▣ 36% show some atrophy when both DM and HTN present

CV Risk Factors and Cognitive Functioning

- ▣ There is cumulative impact of Cardiovascular risk factors on cognitive functioning
- ▣ For each risk factor at NP testing, risk of lower NP performance increased by 23% (Framingham study):
 - HTN
 - DM
 - Cholesterol
 - Smoking
 - Alcohol
 - Obesity
- ▣ More risks, more deficits

Co-Morbidities of Northern Cal KP Dementia Pts (1 million charts; 50T dementia pts)



Preventable Cardiovascular Risk Factors

- ▣ Cigarette smoking
- ▣ Poor nutrition
- ▣ Physical inactivity
- ▣ Excessive alcohol use

- ▣ Hypertension
- ▣ High cholesterol
- ▣ Diabetes
- ▣ Metabolic Syndrome (Insulin resistance)

- ▣ Atherosclerosis → Impaired cerebral blood flow → Brain infarction (stroke)

DM & CV Disease: Intertwined but separate

- ▣ DM and CV disorders are intertwined biomedically.
- ▣ There is little evidence for idea that cognitive impairment associated with DM is consequence of comorbid CV disease.
- ▣ DM per se has an effect on cognition that is independent of CV disease

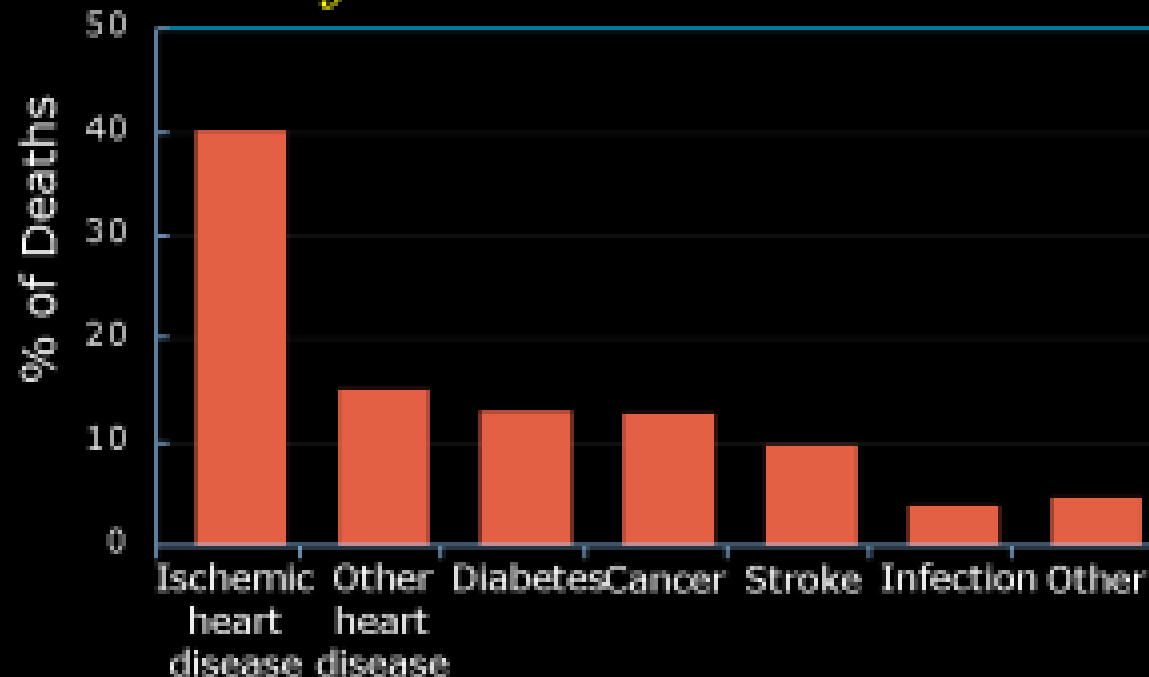
Cardiovascular Disease & DM

- ▣ DM adults have 2x rate of normals:
 - High Blood Pressure
 - High Cholesterol
 - Heart disease
 - Stroke

- ▣ All of these 4 are risk factors for cognitive decline, MCI, and Alzheimer's

Diabetes: Ischemic Heart Disease

Mortality in People with Diabetes *Causes of Death*



Gelss LS et al. In: *Diabetes in America*. 2nd ed. 1995; chap 11.

DM & Heart Disease & Stroke

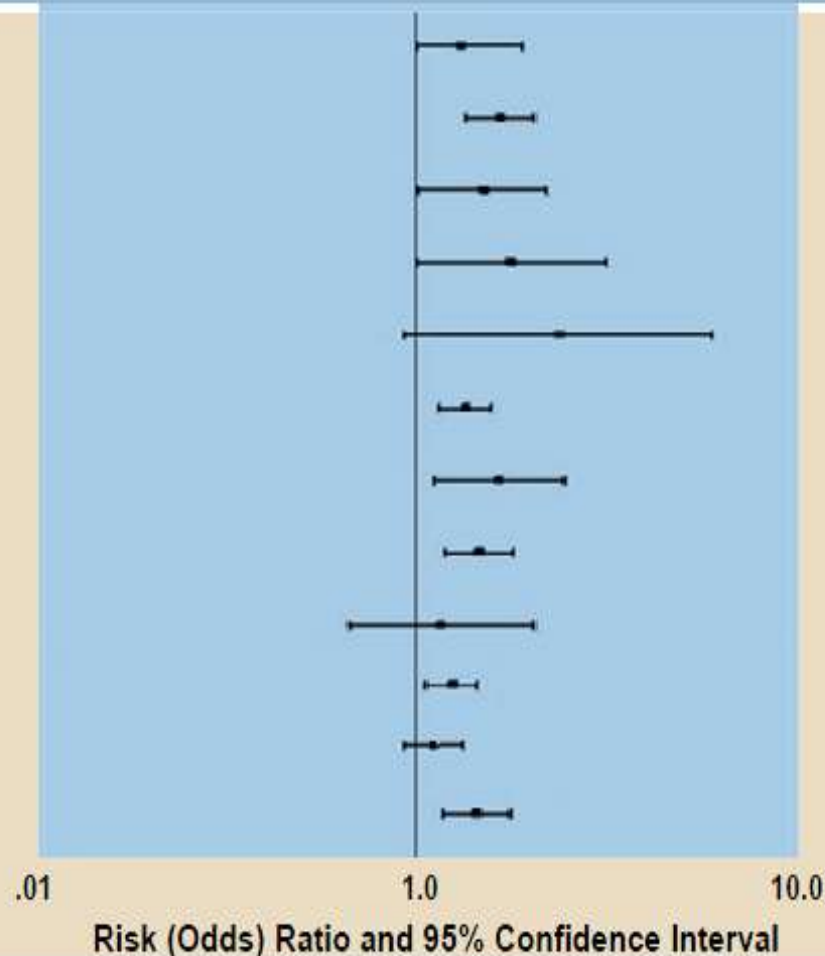
- ▣ Heart disease present in 68% of DM-related death certificates of 65+.
- ▣ Stroke: 16% of DM-related death certificates of 65+.
- ▣
- ▣ DM Adults: heart disease death rates about 2 to 4 times higher
- ▣ **Hypertension:** 67% had blood pressure greater than or equal to 140/90 or used prescription medications for hypertension.

Hypertension and Risk of Dementia

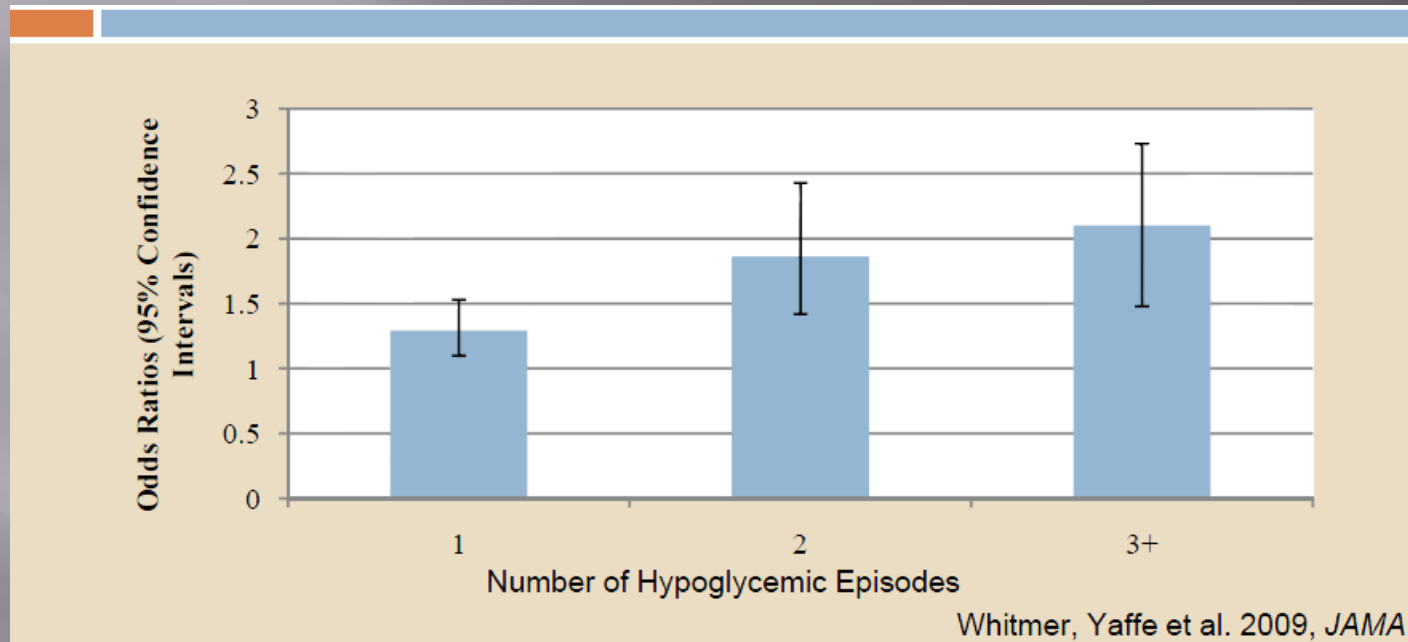
- ▣ Consistent finding between mid-life HTN and dementia
- ▣ Greater BA plaques/tangles in those with mid-life HTN

Diabetes and Likelihood of Dementia

Ott, 1996	Dementia
Leibson, 1997	Dementia
Pelia, 2002	Dementia
Yaffe, 2004	MCI
	Dementia
Logroscino, 2004	MCI
Arvanitakis, 2004	AD
Whitmer, 2005	Dementia
Akomolafe, 2006	AD
Luchsinger, 2007	MCI
Xu, 2009	AD
Rastas, 2010	Dementia



Hypoglycemic Episodes and Dementia in older Type 2 DM



1 episode: 26 % greater risk of dementia

2 episodes: 115 %

3 + episodes: 160 %

Danger of tight glycemic control

MRI in Type 2 Diabetes

- ▣ Brain MRI abnormalities in Type 2 DM:
 - Modest cortical and subcortical atrophy and infarcts are more common
- ▣ Cognitive impairments in Type 2 DM are associated with these MRI abnormalities
- ▣ But no consistent relation with white matter lesions

DM & Atrophy

- Cognitive decline in people with Type 2 Diabetes is likely due to brain atrophy that resembles patterns seen in the early stages of Alzheimer's disease.
- Brain atrophy, rather than cerebrovascular lesions, was likely the primary reason for cognitive impairment associated with T2DM.
- Pts with DM performed less well in certain cognitive tests and had greater shrinkage in specific regions of the brain

Atrophy not related to Ischemic disease

- ▣ Longer duration of diabetes and higher fasting plasma glucose level is associated with brain volume loss, particularly in the gray matter, possibly reflecting direct neurologic insult.
- ▣ Biochemical measures of glycemia were less consistently related to MR imaging changes.
- ▣ Fasting plasma glucose was also inversely correlated with ischemic lesion volume; Hemoglobin A_{1c} level was not associated with any MR imaging measure.
- ▣ Contrary to common clinical belief, in this sample of patients with type 2 diabetes mellitus, there was no association of diabetes characteristics with small vessel ischemic disease in the brain.

Reversible deficits?

- ▣ Type 2 Diabetes cognitive deficits may be reversible.
- ▣ As metabolic control improved at 6 months, so did measures of learning, memory & attention

DM in Elderly

- ▣ 23%+ of people older than 60 have Type 2 diabetes
- ▣ Older DM adults who have:
 - high blood pressure
 - walk slowly
 - lose their balance
 - or believe they're in bad health
- ▣ are significantly more likely to have weaker memory and slower, more executive functioning.

EF and Cognitive Speed Decline Early in DM

- ▣ Study: 41 adults with diabetes and 424 adults in good health, between ages 53 and 90.
- ▣ Healthy adults perform significantly better than adults with DM on two of the five domains tested:
 - executive functioning
 - processing speed
- ▣ Diabetes-linked cognitive deficits appear early and remain stable

DM and psychiatric issues

- ▣ No significant psychological consequences in children and adolescents
- ▣ 8-28% depression in adults (as with chronic disease pts)
- ▣ Twice as likely to have depression, which can complicate diabetes management.
- ▣ In addition, depression is associated with a 60% increased risk of developing type 2 diabetes.

2012 UCSF Health, Aging & Body Composition Study

- ▣ N 3069, over 70; since 1997
- ▣ DM+ at start: had faster cognitive decline
- ▣ Developed it during study worse than those who never had it
- ▣ Those with more severe DM with poor control suffered faster cognitive decline
- ▣ Both duration and severity of DM important

The usual suspects

- ▣ Causes of Cognitive Decline in DM:
 - Aging
 - DM
 - Cardiovascular condition
 - Poor metabolic control

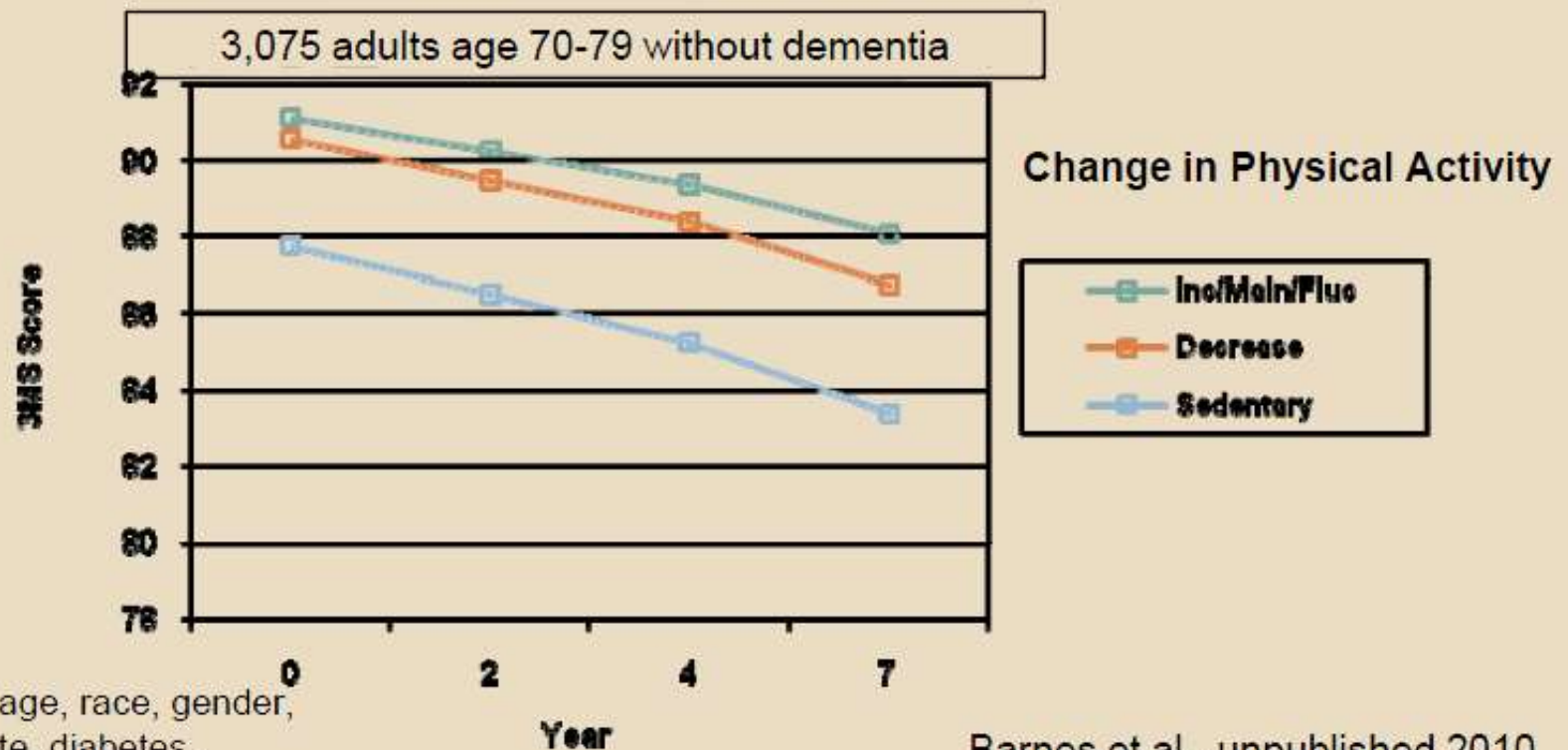
Evidence of some Cognitive Resilience

- ▣ Compelling evidence for adverse cognitive effects due to DM
- ▣ But is there a slowly progressive brain disorder?
- ▣ Type 1 adults:
 - Have peripheral complications
 - but only limited cognitive effects
 - Older Type 1 adults do not show pronounced cognitive decline compared to younger
 - only modest deficits (not clinically relevant)
- ▣ Diabetics appear to have neurocognitive resilience
- ▣ Role of cognitive reserve

Conclusions:

- ▣ DM is associated with altered brain function
- ▣ In most diabetics, there is only subtle cognitive deficits
- ▣ Type 1 DM:
 - modest cognitive deficits in young and middle aged individuals
 - related to poor metabolic control and development of microvascular complications
 - but not due to occurrence of severe hypoglycemic episodes
- ▣ Type 2 DM: both cognitive deficits and brain abnormalities in older pts
- ▣ There is diabetes-related cognitive decline that is clinically relevant in some patients (need NP testing)

Sedentary/Decreasing Activity →→ Faster Cognitive Decline



Adjusted for age, race, gender,
education, site, diabetes,
hypertension, smoking, alcohol

Barnes et al., unpublished 2010

Current Prevention Strategies

▣ REDUCE:

- Poor metabolic control
- Cardiovascular disease (CVD) risk factors
- Obesity/metabolic dysregulation
- Physical inactivity
- Intellectual inactivity
- Sleep disorders
- Depression

Depression and Diabetes

- ▣ Depression is common among people with diabetes and contributes to issues with medication and diet adherence
- ▣ Depression treatment of older adults with diabetes and depression reduces death over a 5-year period by 50 percent.

Use Behavioral Memory system if Poor Executive Functioning

- ▣ If DM creates poor EF temporarily:
- ▣ Need to have alternative procedural memory technique:
 - Don't problem solve
 - Do automatic contracted practice drill
 - ▣ Go to cupboard
 - ▣ Drink Juice, Eat candy
 - ▣ Check blood sugar level

Metformin is Neuroprotective

- ▣ People with type 2 diabetes have double the risk of developing dementia compared to someone without diabetes
- ▣ Over a five-year study period, patients (n = 15,000, age 55+) taking metformin had a 20 percent reduced risk of developing dementia compared to those taking sulfonylureas, thiazolidinediones (TZDs) or insulin.
- ▣ Study author Dr. Rachel Whitmer, an epidemiologist in the division of research at Kaiser Permanente in Oakland, CA, said, "Metformin could have a possible neuroprotective effect in the brain."
- ▣ Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglyceride levels

Most Important Tip : Exercise: Keep moving and Keep your Wits

- ▣ Exercise is the single most powerful and best way to reduce the risk of cognitive decline.
- ▣ Aerobic Exercise: increases size of hippocampus
- ▣ *Spark* by John J. Ratey: The Revolutionary New Science of Exercise and the Brain.

Ten Commandments for Brain Fitness

- I. Thou shalt exercise daily.
- II. Thou shalt minimize risk factors for cerebrovascular disease (HTN, Hyperlipidemia, DM, overweight, smoking)
- III. Thou shalt eat a Mediterranean Diet
- IV. Thou shalt choose thy parents wisely
- V. Thou shalt maintain intellectual engagement throughout life
- VI. Thou shalt cultivate and sustain friendships and good company
- VII. Thou shalt obtain restful sleep
- VIII. Thou shalt enjoy only 1 drink of alcohol
- IX. Thou shalt manage stress effectively
- X. Thou shalt monitor your blood sugar.

References

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- ▣ Vascular Contributions to Cognitive Impairment and Dementia, Philip B. Gorelick, et al., *Stroke*, 2011

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